APPENDIX A:

AMENDMENTS TO THE SPECIFICATION WITH APPROPRIATE EDITING INDICIA

Please replace the specification at page 12, lines 4-14, to read as follows:

FIG. 5. Alignment of the predicted amino acid sequence of human calpain 10a with representative members of the large subunit calpain family. The four domains of the calpains are indicated. This alignment was generated with CLUSTAL X™. rCAPN8 (SEQ ID NO:27) and hCAPN9 (SEQ ID NO:28) denote nCL-2 and -4, respectively. The mouse and rat sequences for calpain 6 (mCAPN10, SEQ ID NO:26) and calpain 8 (rCAPN10, SEQ ID NO:27) are shown. The GenBank accession numbers and sequence ID listings for the sequences shown here are: hCAPN1, X04366, SEQ ID NO:22; hCAPN2, M23254, SEQ ID NO:23; hCAPN3, X85030, SEQ ID NO:24; hCAPN5, Y10552, SEQ ID NO:25; mCAPN6, Y12582, SEQ ID NO:26; rCAPN8, D14479, SEQ ID NO:27; hCAPN9, AF022799, SEQ ID NO:28; and hCAPN10, AF089088, SEQ ID NO:2.

Please replace the specification at page 12, lines 16-20, to read as follows:

FIG. 6. Unrooted phylogenetic tree of calpain large subunit family. Multiple sequence alignment was performed with CLUSTAL X™. The phylogenetic tree was generated using the neighbor joining method based on the number of amino acid substitutions. Branch lengths are proportional to the inferred phylogenetic distances. The tree was drawn using TREEVIEW™.

Please replace the paragraph spanning page 35, lines 22-30 and page 36, lines 1-7 to read as follows:

Once preliminary studies provide evidence for statistical interaction between regions, it is possible to incorporate linkage evidence from one region in assessing evidence for linkage at a second region (or multiple regions) by weighting families according to their evidence for linkage. The multipoint allele-sharing approach described by Kruglyak *et al.* (1996) and

extended by Kong and Cox (1997) to efficiently utilize incomplete information was designed to allow families to be weighted individually, but these original implementations assigned each family equal weight. The inventors' newest extension (GENEHUNTER-PLUS™ v2.0) allows users to specify individual weights for each family based, for example, on pedigree structure, number of affecteds, and/or their evidence for linkage at a particular location. Family-specific weighting can be used to model positive interactions (such as epistasis) by assigning weight 0 to families with 0 or negative linkage scores and weight 1 to families with positive linkage scores ($weight_{0\text{-}1}$), or to model heterogeneity by assigning weight 1 to families with negative linkage scores and weight 0 to families with 0 or positive linkage scores ($weight_{1\text{-}0}$). More complex family-specific weights proportional to the evidence for linkage ($weight_{prop}$) can also be constructed.

Please replace the paragraph at page 53, lines 5-9, to read as follows:

Once this analysis is made, polypeptides can be prepared that contain at least the essential features of the antigenic determinant and that can be employed in the generation of antisera against the polypeptide. Minigenes or gene fusions encoding these determinants can be constructed and inserted into expression vectors by standard methods, for example, using PCR™ methodology.

Please replace the paragraph at page 96, lines 2-6, to read as follows:

A number of template dependent processes are available to amplify the marker sequences present in a given template sample. One of the best known amplification methods is the polymerase chain reaction (referred to as PCR™) which is described in detail in U.S. Patent Nos. 4,683,195, 4,683,202 and 4,800,159, and in Innis *et al.*, 1990, each of which is incorporated herein by reference in its entirety.

Please replace the paragraph at page 96, lines 8-16, to read as follows:

Briefly, in PCR™, two primer sequences are prepared that are complementary to regions on opposite complementary strands of the marker sequence. An excess of deoxynucleoside triphosphates are added to a reaction mixture along with a DNA polymerase, *e.g.*, *Taq*

polymerase. If the marker sequence is present in a sample, the primers will bind to the marker and the polymerase will cause the primers to be extended along the marker sequence by adding on nucleotides. By raising and lowering the temperature of the reaction mixture, the extended primers will dissociate from the marker to form reaction products, excess primers will bind to the marker and to the reaction products and the process is repeated.

Please replace the paragraph at page 96, lines 18-23, to read as follows:

A reverse transcriptase PCR™ amplification procedure may be performed in order to quantify the amount of mRNA amplified. Methods of reverse transcribing RNA into cDNA are well known and described in Sambrook *et al.*, 1989. Alternative methods for reverse transcription utilize thermostable, RNA-dependent DNA polymerases. These methods are described in WO 90/07641 filed December 21, 1990. Polymerase chain reaction methodologies are well known in the art.

Please replace the paragraph spanning page 96, lines 25-30 and page 97, lines 1-2 to read as follows:

Another method for amplification is the ligase chain reaction ("LCR"), disclosed in EPA No. 320 308, incorporated herein by reference in its entirety. In LCR, two complementary probe pairs are prepared, and in the presence of the target sequence, each pair will bind to opposite complementary strands of the target such that they abut. In the presence of a ligase, the two probe pairs will link to form a single unit. By temperature cycling, as in PCR™, bound ligated units dissociate from the target and then serve as "target sequences" for ligation of excess probe pairs. U.S. Patent 4,883,750 describes a method similar to LCR for binding probe pairs to a target sequence.

Please replace the paragraph at page 106, lines 5-10, to read as follows:

All forms of RNA fingerprinting by PCR™ are theoretically similar but differ in their primer design and application. The most striking difference between differential display and other methods of RNA fingerprinting is that differential display utilizes anchoring primers that

hybridize to the poly A tails of mRNAs. As a consequence, the PCR products amplified in differential display are biased towards the 3' untranslated regions of mRNAs.

Please replace the paragraph at page 107, lines 3-9, to read as follows:

Reverse transcription (RT) of RNA to cDNA followed by relative quantitative PCR<u>TM</u> (RT-PCR<u>TM</u>) can be used to determine the relative concentrations of specific mRNA species isolated from type 2 diabetes patients. By determining that the concentration of a specific mRNA species varies, it is shown that the gene encoding the specific mRNA species is differentially expressed. This technique can be used to confirm that mRNA transcripts shown to be differentially regulated by RNA fingerprinting are differentially expressed in type 2 diabetes.

Please replace the paragraph at page 107, lines 11-21, to read as follows:

In PCR<u>TM</u>, the number of molecules of the amplified target DNA increase by a factor approaching two with every cycle of the reaction until some reagent becomes limiting. Thereafter, the rate of amplification becomes increasingly diminished until there is no increase in the amplified target between cycles. If a graph is plotted in which the cycle number is on the X axis and the log of the concentration of the amplified target DNA is on the Y axis, a curved line of characteristic shape is formed by connecting the plotted points. Beginning with the first cycle, the slope of the line is positive and constant. This is said to be the linear portion of the curve. After a reagent becomes limiting, the slope of the line begins to decrease and eventually becomes zero. At this point the concentration of the amplified target DNA becomes asymptotic to some fixed value. This is said to be the plateau portion of the curve.

Please replace the paragraph at page 107, lines 23-30 and page 108, lines 1-3 to read as follows:

The concentration of the target DNA in the linear portion of the PCR<u>TM</u> amplification is directly proportional to the starting concentration of the target before the reaction began. By determining the concentration of the amplified products of the target DNA in PCR<u>TM</u> reactions that have completed the same number of cycles and are in their linear ranges, it is possible to determine the relative concentrations of the specific target sequence in the original DNA mixture. If the DNA mixtures are cDNAs synthesized from RNAs isolated from different tissues

or cells, the relative abundances of the specific mRNA from which the target sequence was derived can be determined for the respectivetissues or cells. This direct proportionality between the concentration of the PCR™ products and the relative mRNA abundances is only true in the linear range of the PCR™ reaction.

Please replace the paragraph at page 108, lines 4-9, to read as follows:

The final concentration of the target DNA in the plateau portion of the curve is determined by the availability of reagents in the reaction mix and is independent of the original concentration of target DNA. Therefore, the first condition that must be met before the relative abundances of a mRNA species can be determined by RT-PCR™ for a collection of RNA populations is that the concentrations of the amplified PCR products must be sampled when the PCR reactions are in the linear portion of their curves.

Please replace the paragraph at page 108, lines 20-30, to read as follows:

Most protocols for competitive PCR™ utilize internal PCR™ standards that are approximately as abundant as the target. These strategies are effective if the products of the PCR™ amplifications are sampled during their linear phases. If the products are sampled when the reactions are approaching the plateau phase, then the less abundant product becomes relatively over represented. Comparisons of relative abundances made for many different RNA samples, such as is the case when examining RNA samples for differential expression, become distorted in such a way as to make differences in relative abundances of RNAs appear less than they actually are. This is not a significant problem if the internal standard is much more abundant than the target. If the internal standard is more abundant than the target, then direct linear comparisons can be made between RNA samples.

Please replace the paragraph spanning page 123, lines 28-30 and page 124, lines 1-5 to read as follows:

The calpain-like protein and G-protein coupled receptor were examined for sequence motifs using the program PROSITE (~~http://www.~~ebi.ac.uk). Multiple alignment of amino acid

sequences was carried using the CLUSTAL X™ software package (http://www.igbmc.u-strasbg.fr/BioInfo/clustal). Phylogenetic trees were constructed using the neighbor joining method based on the number of amino acid substitutions. Bootstrap tests were performed using a random number generator and number of bootstrap trials of 1,000 and 10,000, respectively. The tree was drawn using the TREEVIEW™ package (http://taxonomy.zoology.gla.ac.uk/rod/treeview).

Please replace the paragraph spanning page 126, lines 23-29 and page 127, lines to read as follows:

Linkage analyses were conducted using a version of GENEHUNTER™ (Kruglyak *et al.*, 1996) modified to allow assessment of the evidence for linkage that is not conservative in the presence of missing data Kong and Cox, 1997), and all analyses were conducted using the S(pairs) scoring function. These analyses were facilitated by development of a recent extension that allows weights for families to be specified. Thus, families in which no member was typed were assigned weight 0 and similarly, families in which the single typed member had a non-associated genotype were assigned weight 0, while families in which the single typed individual had an associated genotype were assigned weight 1.

Please replace the paragraph at page 143, lines 21-30, to read as follows:

Simulation studies were used to assess the significance of the increase in lod score at *CYP19* using the weight$_{0-1}$ family weighting with respect to the evidence for linkage at *NIDDM1*. At *D2S140* there were 95 families with positive NPL scores and 75 families with 0 or negative NPL scores. Simulations based on the weight$_{0-1}$, or weight$_{1-0}$ family weighing can be rapidly conducted using the extension which allows families to be weighted individually. The basic GENEHUNTER™ analysis need be conducted only once on the actual data (in this case, from chromosome 15), and then many replicate weighting files can be generated randomly (in this example, 95 randomly chosen families are given weight and the remaining 75 families are given weight 0) and used to calculate the final lod scores.

Please replace the paragraph at page 144, lines 1-6, to read as follows:

The software described in this manuscript is distributed as GENEHUNTER-PLUS™ (version 2.0 or later) and is available *via* anonymous ftp at galton.uchicago.edu on the /pub/kong directory. The allele-sharing method which is used is described in Kong and Cox (1997) and version 2.0 introduces an option to provide a family-specific weight in the lod score computation.

APPENDIX B:
CLEAN COPY OF THE SPECIFICATION AFTER AMENDMENT

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APPENDIX C:

AMENDMENTS TO THE CLAIMS WITH APPROPRIATE EDITING INDICIA

18. (Amended) A method of screening for a modulator of calpain 10 function comprising:
    a) obtaining a calpain 10 polypeptide;
    b) determining a standard activity profile of the calpain 10 polypeptide;
    c) contacting the calpain 10 polypeptide with a putative modulator; and
    d) assaying for a change in the standard activity profile.

19. (Amended) The method of claim 18, wherein the calpain 10 polypeptide [is a clapiain 10 polypeptide] comprises amino acid 1 to 47 of SEQ ID NO:2.

20. (Amended) The method of claim 18, wherein obtaining the calpain 10 polypeptide comprises expressing the polypeptide in a host cell.

21. (Amended) The method of claim 20, wherein the calpain 10 polypeptide is isolated away from the host cell prior to contacting the calpain 10 polypeptide with the putative modulator.

50. (Amended) The method of claim 49, wherein the synthetic substrate is [Suc-Leu-Tyr-AMC] Suc-Leu-Tyr-amidomethylcoumarin (AMC).

51. (Amended) A method of screening for a modulator of calpain 10 function comprising:
    a) obtaining an calpain 10 polypeptide;
    b) contacting the calpain 10 polypeptide with a putative modulator; and
    c) assaying for modulation of calpain 10 function by the putative modulator.

52. (Amended) The method of claim 51, wherein the calpain 10 polypeptide [is a calpain 10 polypeptide] comprises the amino acid sequence of SEQ ID NO: 2.

53. (Amended) The method of claim 52, wherein the calpain 10 polypeptide has a sequence comprising amino acid 1 to 47 of SEQ ID NO:2[, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, or SEQ ID NO:18].

54. (Amended) The method of claim 51, further comprising determining a standard activity profile of the calpain 10 polypeptide.

56. (Amended) The method of claim 55, wherein the synthetic substrate is [Suc-Leu-Tyr-AMC] Suc-Leu-Tyr-amidomethylcoumarin (AMC).

57. (Amended) The method of claim 55, wherein assaying for modulation of calpain 10 function comprises assaying for a change in the standard activity profile.

58. (Amended) The method of claim 51, wherein obtaining the calpain 10 polypeptide comprises expressing the polypeptide in a host cell.

59. (Amended) The method of claim 58, wherein the calpain 10 polypeptide is isolated away from the host cell prior to contacting the calpain polypeptide with the putative modulator.

60. (Amended) The method of claim 51, wherein obtaining the calpain 10 polypeptide comprises obtaining a cell containing the polypeptide.

114. (New) The method of claim 18, wherein the calpain 10 polypeptide comprises the amino acid sequence of SEQ ID NO:2

APPENDIX D:

COPY OF PENDING CLAIMS AFTER AMENDMENTS

18. A method of screening for a modulator of calpain 10 function comprising:
    a) obtaining a calpain 10 polypeptide;
    b) determining a standard activity profile of the calpain 10 polypeptide;
    c) contacting the calpain 10 polypeptide with a putative modulator; and
    d) assaying for a change in the standard activity profile.

19. The method of claim 18, wherein the calpain 10 polypeptide comprises amino acid 1 to 47 of SEQ ID NO:2.

20. The method of claim 18, wherein obtaining the calpain 10 polypeptide comprises expressing the polypeptide in a host cell.

21. The method of claim 20, wherein the calpain 10 polypeptide is isolated away from the host cell prior to contacting the calpain 10 polypeptide with the putative modulator.

49. The method of claim 19, wherein the standard activity profile of the calpain 10 polypeptide is determined by measuring the binding of the calpain 10 polypeptide to a synthetic substrate.

50. The method of claim 49, wherein the synthetic substrate is Suc-Leu-Tyr-amidomethylcoumarin (AMC).

51. A method of screening for a modulator of calpain 10 function comprising:
    a) obtaining an calpain 10 polypeptide;
    b) contacting the calpain 10 polypeptide with a putative modulator; and
    c) assaying for modulation of calpain 10 function by the putative modulator.

52. The method of claim 51, wherein the calpain 10 polypeptide comprises the amino acid sequence of SEQ ID NO: 2.

53. The method of claim 52, wherein the calpain 10 polypeptide has a sequence comprising amino acid 1 to 47 of SEQ ID NO:2,

54. The method of claim 51, further comprising determining a standard activity profile of the calpain 10 polypeptide.

55. The method of claim 54, wherein the standard activity profile of the calpain 10 polypeptide is determined by measuring the binding of the calpain 10 polypeptide to a synthetic substrate.

56. The method of claim 55, wherein the synthetic substrate is Suc-Leu-Tyr-amidomethylcoumarin (AMC).

57. The method of claim 55, wherein assaying for modulation of calpain 10 function comprises assaying for a change in the standard activity profile.

58. The method of claim 51, wherein obtaining the calpain 10 polypeptide comprises expressing the polypeptide in a host cell.

59. The method of claim 58, wherein the calpain 10 polypeptide is isolated away from the host cell prior to contacting the calpain polypeptide with the putative modulator.

60. The method of claim 51, wherein obtaining the calpain 10 polypeptide comprises obtaining a cell containing the polypeptide.

61. The method of claim 60, wherein the cell is a pancreatic cell, a muscle cell, an adipose cell, or a liver cell.

62. The method of claim 61, wherein the cell is a pancreatic cell.

63. The method of claim 62, wherein the pancreatic cell is comprised in an isolated pancreatic islet.

64. The method of claim 62, wherein the cell is a β-cell.

114. The method of claim 18, wherein the calpain 10 polypeptide comprises the amino acid sequence of SEQ ID NO:2